Exhibit 6

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Inhaled Glucocorticosteroid and Long-Acting β_2-Adrenoceptor Agonist Single-Inhaler Combination for Both Maintenance and Rescue Therapy

A Paradigm Shift in Asthma Management

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Abstract

Despite aggressive fixed-dose (FD) combination therapy with inhaled glucocorticosteroids (ICS) and long acting β_2-adrenoceptor agonists (LABA), many patients with asthma remain suboptimally controlled, based on the need for rescue therapy and rates of severe exacerbations. The strategy of adjustable maintenance dosing (AMD) involves adjustment of the maintenance dose, (using a single combination [budesonide/formoterol] inhaler, Symbicort®) in response to variability of asthma control over time. The AMD strategy, like the FD approach, involves the use of a short-acting β_2-adrenoceptor agonist (SABA) for rapid relief of bronchospasm. The dose-response characteristics of budesonide/formoterol make the AMD strategy a feasible option that cannot be exploited with the combination of salmeterol/fluticasone propionate (Advair®). Several studies suggest that the AMD strategy is superior to a FD approach in terms of overall asthma control.

Budesonide/formoterol in a single inhaler is as effective as albuterol (salbutamol) for relief of acute asthma episodes, a feature that makes it possible to use this combination for both maintenance and reliever therapy without the need for the use of a SABA. The single-inhaler strategy has been shown to be safe and more efficacious than FD therapy. In particular, the COSMOS study has demonstrated that exacerbation burden is reduced more effectively when the combination (budesonide/formoterol) single inhaler is used for both maintenance and relief compared with FD therapy with salmeterol/fluticasone and albuterol for rescue in patients with moderate-to-severe asthma. These findings suggest that we will have to reconsider our definition of reliever therapy for patients that require long-term therapy with combination ICS and LABA.

The concept of single-inhaler therapy represents a paradigm shift in asthma management that has been validated in several large studies involving thousands of patients. The single-inhaler strategy represents one of the most significant advances in asthma management in many years, and one that appears ideal for adoption in primary care.

Asthma is a chronic inflammatory disease of the airways associated with variable airflow obstruction and symptoms that include cough, wheezing, chest tightness, and shortness of breath.[1] Inhaled glucocorticosteroids (ICS) are considered first-line therapy for suppression of airway inflammation[1,2] and disease stabilization in patients with persistent symptoms. If asthma is not well controlled on low-to-moderate doses of ICS, additional therapy should be initiated; a long-acting β_2-adrenoceptor agonist (LABA) should be considered as the add-on therapy of choice.

A combination of LABA and inhaled glucocorticosteroid, in a single inhaler, represents an important advancement in the management of asthma. It has been known for some time[3-7] that in addition to being more convenient than separate inhalers, the combination inhalers achieve asthma control at lower doses of ICS compared with ICS alone. This strategy is also more likely to

prevent patients from over-relying on their reliever medication (e.g. a rapid long- or short-acting β_2-adrenoceptor agonist [SABA]), thereby minimizing the likelihood of ICS under-utilization.

Currently, two combination products – Symbicort®[1] (budesonide/formoterol) and Advair®/Seretide® (fluticasone propionate/salmeterol) – are available in various parts of the world. At present both combination products are utilized using a twice daily maintenance dosage strategy, with a SABA used for relief of asthma symptoms. Given the dose-response characteristics of formoterol[8] and budesonide,[9] the maintenance dose of budesonide/formoterol can be adjusted according to fluctuations in asthma control using a single inhaler. This strategy is known as adjustable maintenance dosage (AMD), and utilizes a SABA as reliever therapy. AMD is not indicated with fluticasone propionate/salmeterol. Recent studies, researching a novel treatment approach where budesonide/formoterol is used as both maintenance and reliever therapy (i.e. where SABA is no longer used as a reliever), suggest that this treatment approach may provide superior asthma control compared with fixed dosage strategies with either budesonide/formoterol or fluticasone propionate/salmeterol. This article reviews the evolution of combination therapy in asthma management and provides an evidence-based perspective on the strategy of single-inhaler therapy consisting of a corticosteroid and a LABA as both maintenance and reliever therapy in individuals with asthma.

1. Comparison of Fixed and Adjustable Maintenance Dose Strategies

Two landmark studies[5,6] utilizing a fixed dose (FD) strategy involving the administration of budesonide and formoterol (using separate inhalers) revealed that this combination was associated with fewer exacerbations compared with a 2- or 4-fold higher dose of ICS. An earlier FD study,[3] which utilized the combination of salmeterol and beclomethasone dipropionate (BDP), was not designed to examine severe exacerbations as a primary endpoint, although salmeterol use was associated with significant improvements in lung function and other indices of asthma control. A prospective, randomized, placebo-controlled study[10] evaluating the influence of salmeterol in combination with ICS (using separate inhalers) on asthma control revealed that exacerbations were not reduced by salmeterol despite improvements in lung function, reliever medication use, and nocturnal awakenings.

The AMD strategy is in keeping with current asthma management guidelines,[1,2] which recommend that after achieving desirable control, asthma medications should be titrated to the lowest dose that maintains control. The AMD regimen allows patients to adjust the maintenance dose of ICS and LABA (in a single inhaler) in response to changes in their level of symptoms – a strategy that employs use of an action plan and ongoing communication between patient and physician. Since both budesonide and formoterol are effective at low doses and exhibit dose-response characteristics over the dose ranges studied clinically,[8,9] this combination is well suited for AMD therapy.

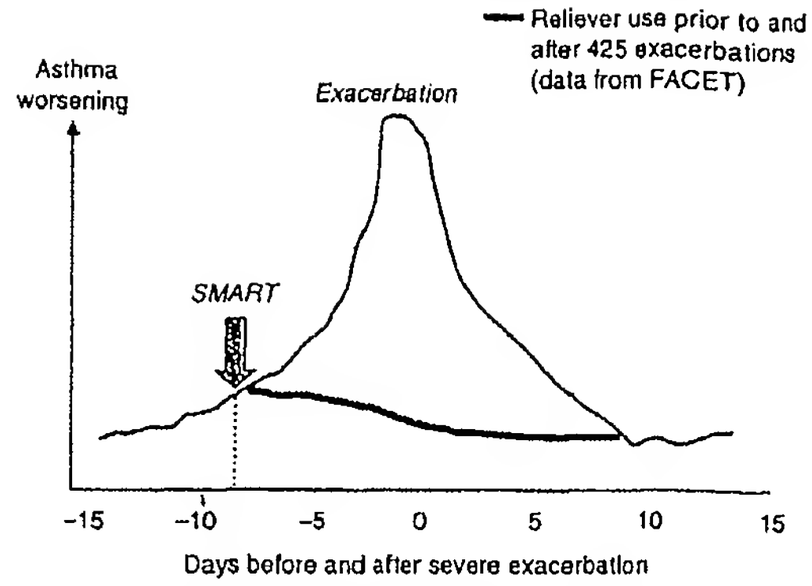

Fig. 1. Reliever use as a function of asthma worsening over time (adapted from Tattersfield et al.,[20] with permission). **FACET** = Formoterol and Corticosteroids Establishing Therapy;[5] **SMART** = Symbicort® Maintenance and Reliever Therapy.

A number of open-label studies[11-13] have helped to clarify the potential benefits of AMD therapy compared with FD therapy. One of the first studies, by Stallberg et al.,[13] revealed that compared with FD (budesonide/formoterol), AMD with budesonide/formoterol reduced exacerbations (6.2% vs 9.5%, $p < 0.05$), reduced daily inhalations of budesonide/formoterol (2.35 vs 3.95, $p < 0.001$), and was associated with lower costs for asthma care over a 6-month period. In a similar study, Fitzgerald et al.[11] reported that AMD with budesonide/formoterol provided more effective asthma control than FD, with a lower overall drug dose and reduced total costs. Aalbers et al.[12] compared budesonide/formoterol (160/4.5μg) AMD versus budesonide/formoterol (160/4.5μg) FD and salmeterol/fluticasone (Seretide® diskus 50/250μg) FD. These authors reported that the odds ratio for achieving a well-controlled asthma week did not differ between groups during the initial 4-week double-blind period, when the FD regimens were utilized. By contrast, during the 6-month open extension period, budesonide/formoterol AMD increased the odds of achieving a well controlled asthma week compared with budesonide/formoterol FD ($p < 0.049$) in association with a 15% reduction in average study drug use. Furthermore, budesonide/formoterol AMD therapy resulted in a lower exacerbation rate over the study period, 40% lower than with salmeterol/fluticasone FD ($p = 0.018$). Other

1 The use of trade names is for product identification purposes only and does not imply endorsement.

studies[14-17] have shown that an AMD strategy may provide similar asthma control compared with a FD strategy at a lower total daily dose. Only one study[18] has shown that FD combination therapy with salmeterol/fluticasone 50/250µg is superior to AMD with budesonide/formoterol. In this study, the majority of patients (82%) on AMD used a minimum of one inhalation once daily, while in the studies described above,[11-13] patients on the AMD strategy used a minimum maintenance treatment of one inhalation twice daily. The results of this study[18] suggest that there is a minimum maintenance dose necessary to prevent deterioration of asthma control.

2. Single-Inhaler Therapy

Despite marked improvement in asthma control reported with the use of combination ICS and LABA therapy,[4,5,7] optimal asthma control is not achieved in many patients based on the requirement for SABA therapy and exacerbation rates. These findings suggest that fluctuations in control represent an inherent feature of the natural history of asthma and may in part be related to inadequate anti-inflammatory therapy. Traditionally, patients have been instructed to increase their SABA use to relieve symptoms. Formoterol, a rapid long-acting bronchodilator, used as a reliever has a similar safety profile to albuterol (salbutamol) and is associated with fewer asthma symptoms and exacerbations than albuterol.[19] Furthermore, budesonide/formoterol in a single inhaler is as effective as albuterol in relieving acute asthma episodes in adults and adolescents.[8] These data have provided important information in the development of the single inhaler concept, a new treatment strategy where budesonide/formoterol is taken as both maintenance and reliever therapy, without the requirement for the use of SABA.

Data from the Tattersfield et al.[20] study suggest that prior to a severe exacerbation (figure 1), there is a period of 5–7 days during which patients experience deteriorating symptoms and lung function. This period represents an opportunity to intervene early with an increase in ICS that is coupled with the rapid acting LABA, formoterol, which has a systemic adverse effect profile similar to a SABA.[21] The recent landmark trial by O'Byrne at al.[22] demonstrated that budesonide/formoterol 80/4.5µg twice daily plus as-needed budesonide/formoterol 80/4.5µg was superior to budesonide/formoterol 80/4.5µg twice daily plus as-needed SABA and to budesonide 320µg twice daily plus as-needed SABA in prolonging the time to first severe exacerbation in adolescents and adults; similar results were seen in children (4–11 years old) given half the maintenance dose once daily at night. This study also demonstrated that single-inhaler therapy with budesonide/formoterol significantly reduced total severe exacerbations requiring medication intervention, and oral corticosteroid use compared with either budesonide/formoterol FD or a 4-fold higher dose of budesonide for maintenance therapy, both using SABA for relief. Of particular interest is the finding that the mean daily dose of budesonide with single-inhaler therapy (240 µg/day for adults and 126 µg/day in children) was less than that in the budesonide plus SABA group (640 µg/day for adults and 320 µg/day in children) despite superior asthma control when budesonide/formoterol single inhaler was used for both maintenance and relief. This finding suggests that it is (in part) the timing of the ICS dose in response to worsening asthma symptoms, rather than the total daily dose of ICS, that determines efficacy. Scicchitano et al.[23] have shown that budesonide/formoterol as maintenance (160/4.5µg, two inhalations once daily) and relief is superior to budesonide maintenance (160µg, two inhalations twice daily) and SABA as relief in prolonging the time to first exacerbation. In this latter study the number needed-to-treat to prevent one severe exacerbation (defined as hospitalization/emergency room treatment or systemic corticosteroid use due to asthma worsening or a fall in the morning peak expiratory flow ≤70% of baseline on two consecutive days) was 5.

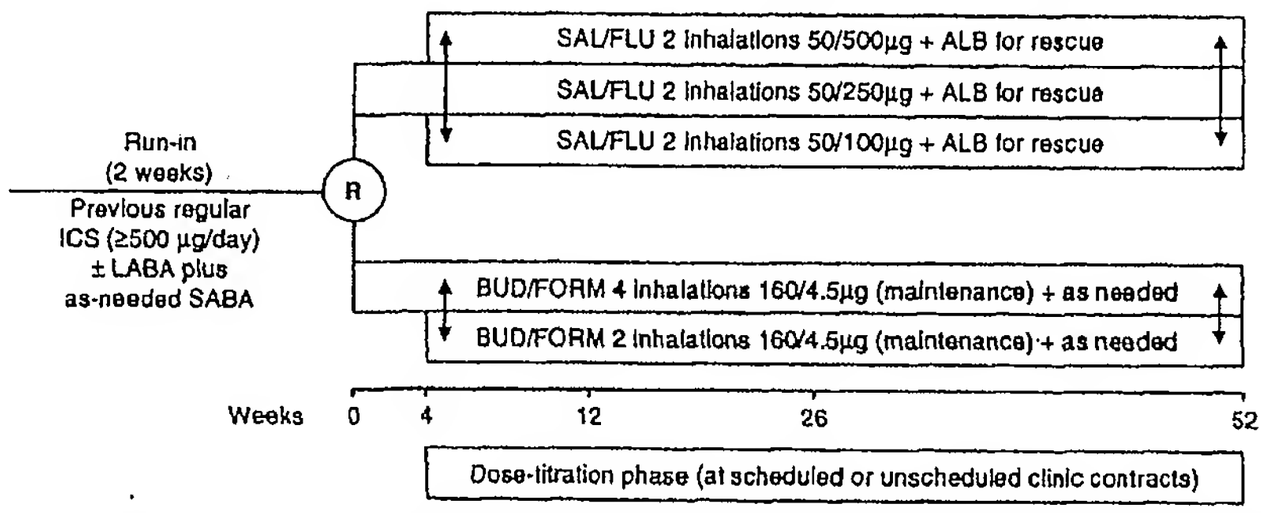

Fig. 2. Study design (reproduced from Vogelmeier et al.,[24] with permission). **ALB** = albuterol (salbutamol); **BUD/FORM** = budesonide/formoterol; **ICS** = inhaled glucocorticosterold; **LABA** = long-acting β_2-adrenoceptor agonist; **R** = randomization; **SABA** = short-acting β_2-adrenoceptor agonist; **SAL/FLU** = salmeterol/fluticasone propionate.

Table I. Baseline characteristics of patients enrolled in the COSMOS study. Data are presented as mean (range), unless otherwise stated (reproduced from Vogelmeier et al.,[24] with permission)

Characteristic	SAL/FLU + albuterol (salbutamol)	BUD/FORM maintenance + as needed
Patients (no.)	1076	1067
Sex (M/F)	429/647	451/616
Age (y)	45 (12–84)	45 (12–80)
Asthma duration (y)	12 (0–74)	13 (1–75)
FEV_1 pre-terbutaline (% predicted)	73 (28[a]–100[a])	73 (39–115[a])
FEV_1 reversibility (%)	13	13
ICS dose at entry (mg/day)	881 (400[b]–3000)	888 (50[b] –2000)
Baseline ICS medication type (% patients BUD/FLU/BDP)	63/24/13	60/25/15
Inhaled LABA use at study entry [no. of patients (%)]	409 (38)	402 (38)
Reliever use (inhalations/24h)	2.7 (0.3[b]–33.7)	2.6 (0.2[b]–10.7)
Use of ≤4 inhalations of as-needed medication/week (% patients)	5	5
Overall ACQ-5 score	1.87 (0.00–5.00)	1.86 (0.00–5.20)
Overall AQLQ(S) score	4.95 (1.19–7.00)	4.97 (1.75–7.00)

a Mean not adjusted for type of ICS or inhaler choice; minimum doses of ICS stipulated at entry were: BUD 500 µg/day, FLU 500 µg/day, and BDP 1000 µg/day for either metered or delivered doses.

b Deviation from inclusion criteria (included in the intention-to-treat population).

ACQ-5 = Asthma Control Questionnaire 5-item score; **AQLQ(S)** = Asthma Quality of Life Questionnaire (Standardized); **BDP** = beclomethasone dipropionate; **BUD** = budesonide; **FLU** = fluticasone propionate; **FORM** = formoterol; **ICS** = inhaled corticosteroid; **LABA** = long-acting β_2-agonist; **SAL** = salmeterol.

These studies [22,23] underscore the potential to utilize a simple and practical asthma management approach that is associated with a high level of efficacy in patients with moderate-to-severe asthma. These studies also suggest that rescue therapy with budesonide/formoterol may be associated with more rapid stabilization of control during periods of asthma worsening. It is important to note that single-inhaler therapy is also referred to as 'Symbicort® Maintenance and Reliever Therapy' (SMART).[23] It is not known whether this strategy is effective in all patients with asthma, including non-compliant patients and individuals who are bad perceivers of asthma control.

3. The COSMOS Study

3.1 Study Design

The COSMOS Trial[24] represents the first attempt to compare the single inhaler strategy versus a FD strategy utilizing a real-life study design. This 12-month randomized, parallel group, open-label, dose titration study compared the effectiveness and safety of budesonide/formoterol for maintenance plus relief to a FD strategy using salmeterol/fluticasone for maintenance plus salbutamol for relief. A total of 2143 patients with moderate-to-severe symptomatic asthma (mean FEV_1 73% predicted, mean ICS 884 µg/day) were studied (table I). During a 2-week run-in period, patients used their existing ICS (and LABA, if appropriate) and as-needed reliever medication. Thereafter, patients were randomized to treatment with either budesonide/formoterol 160/4.5µg two inhalations twice daily plus additional inhalations for relief of asthma symptoms (single-inhaler therapy) or salmeterol/fluticasone 50/250µg twice daily plus albuterol as a reliever. The maintenance doses (moderate) for each combination were chosen to reflect recommendations in current guidelines.[1,2] After 4 weeks of therapy, asthma control was assessed in both groups by physicians at a scheduled study visit, and onwards either at a scheduled clinic visit or an unscheduled contact. In keeping with routine clinical practice, maintenance therapy in both groups was titrated up or down to improve control or to maintain asthma control at the lowest effective dose (figure 2). Furthermore, patients were not required to keep daily diary cards, and reversibility of airflow obstruction was not a requirement for inclusion (a strategy that would tend to avoid selecting patients more likely to respond to increases in LABA therapy).[25] Finally, titration of maintenance medication was left to physicians' judgment and was not protocol driven.

Patients reported maintenance and reliever medication use during the preceding 2 weeks of each clinic visit; total ICS dose was calculated from the prescribed maintenance dose and self-reported reliever medication use (only for the budesonide/formoterol

group). Scheduled visits were infrequent, to mimic real life clinical practice. Other assessments included measurement of FEV_1, Asthma Quality of Life Questionnaire, and Asthma Control Questionnaire 5-item version.

3.2 Primary Endpoint

The primary endpoint was the time to first severe exacerbation defined as a deterioration in asthma resulting in hospitalization/emergency room (ER) treatment, oral corticosteroids for ≥3 days or an unscheduled visit (patient-initiated) leading to treatment change. Severe exacerbations excluding unscheduled patient-initiated visits not resulting in hospitalization/ER treatment or oral corticosteroid therapy as well as hospitalization/ER treatment alone were analyzed on an *a priori* basis.

3.3 Results and Discussion

Single-inhaler therapy with budesonide/formoterol reduced the risk of a severe exacerbation by 25% ($p = 0.008$), or 23% when unscheduled clinic visits were excluded ($p = 0.025$) compared with salmeterol/fluticasone. The time to first exacerbation was prolonged with the single-inhaler strategy ($p = 0.005$), even when unscheduled clinic visits were excluded ($p = 0.017$). The total rate of severe exacerbations was reduced by 22% with the single-inhaler therapy ($p = 0.0025$; figure 3). Single-inhaler therapy with budesonide/formoterol was associated with 38% less reliever medication use than salmeterol/fluticasone ($p < 0.001$). The mean number of prescribed inhalers per patient per year was 12.7 in the single-inhaler group compared with 16.6 in the salmeterol/fluticasone group.

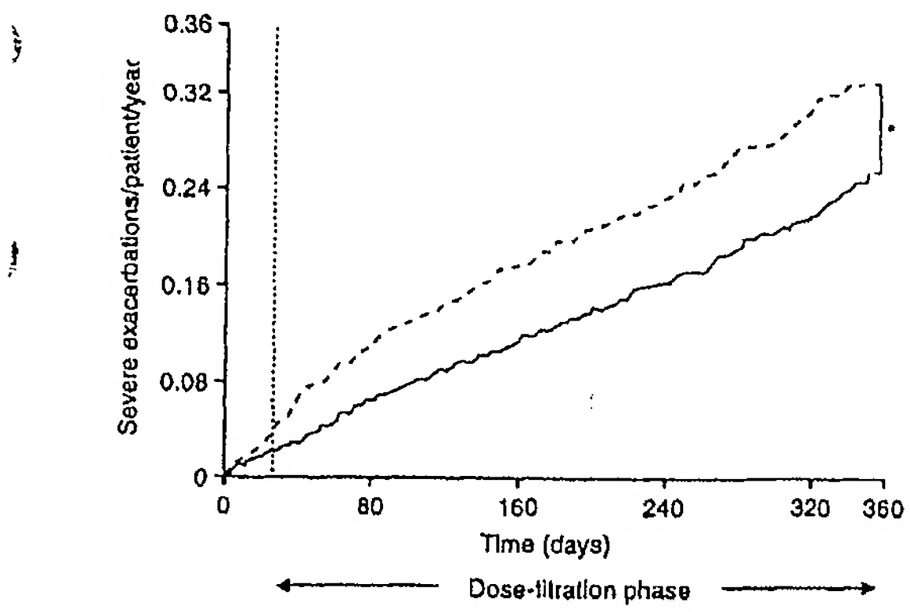

Fig. 3. Cumulative rate plot of time to first and repeat severe asthma exacerbation in both treatment groups (dashed line indicates salmeterol/fluticasone propionate and albuterol [salbutamol] for rescue; solid line indicates budesonide/formoterol maintenance and as needed). The vertical dotted line marks the start of the dose-titration phase (reproduced from Vogelmeier et al.,[24] with permission). * $p = 0.0025$ (Poisson regression analysis of the rate of exacerbations).

A small statistically significant difference in post-bronchodilator FEV_1 was noted in favor of patients in the single-inhaler group (budesonide/formoterol). Health-related quality of life improved from baseline in both groups but there was no statistically significant difference between groups.[24] In both groups, patients used a similar mean total daily dose of budesonide or fluticasone propionate, averaged over the entire treatment period: 562µg (maintenance) + 91µg (for relief of symptoms) for budesonide/formoterol patients versus 583µg (maintenance only) for salmeterol/fluticasone propionate patients. Expressed as equivalent BDP doses, the corresponding values for budesonide/formoterol and salmeterol/fluticasone propionate were 1019 µg/day (maintenance and relief) and 1166 µg/day (maintenance only), respectively. In patients with high reliever use (>4 inhalations/day) the mean total daily dose of ICS was budesonide 910 µg/day (BDP equivalent 1420 µg/day) versus fluticasone propionate 701 µg/day (BDP equivalent 1402 µg/day). Throughout the study, the majority of patients (55%) in the salmeterol/fluticasone propionate group used two different strengths of maintenance inhaler plus albuterol inhaler compared with a single inhaler (of the same strength) for both maintenance and reliever therapy in the budesonide/formoterol group. Single-inhaler therapy with budesonide/formoterol was associated with fewer oral corticosteroid days (≈1000 fewer) and hospital days (35 fewer) compared with salmeterol/fluticasone propionate. In both groups, most patients (76% vs 66% for the budesonide/formoterol and salmeterol/fluticasone propionate groups, respectively) used a maximum of four inhalations per week for relief of symptoms, at study completion. The cost of medication was comparable between the two groups. Both treatments were well tolerated with no notable differences between the groups in number or severity of adverse events.

The use of an open-label design[24] permitted an evaluation of how the single-inhaler concept compared with the FD strategy with salmeterol/fluticasone propionate; the latter potentially requiring three separate maintenance inhalers for dose titration and an additional inhaler for the relief of asthma symptoms.

The use of a single inhaler (budesonide/formoterol) for both maintenance and reliever therapy represents a significant paradigm shift in asthma management that is simple and effective. These features make this strategy particularly appealing for adoption in primary care. The use of a single inhaler for both maintenance and reliever therapy appears to fit well with normal patient behavior, which includes the use of more reliever medication when asthma control declines. When used for symptom relief, the inhaler – which contains an ICS and a rapid acting LABA – both provide relief of acute bronchospasm and eliminates the possibili-

ty of delayed ICS adjustments during periods of asthma deterioration. Interestingly, the study by Woude et al.[26] suggests that during methacholine-provoked bronchoconstriction, budesonide/formoterol induces bronchodilation that is more rapid in onset than with salmeterol/fluticasone, resulting in a significantly greater reduction in dyspnea with budesonide/formoterol.

The benefits observed with the single-inhaler strategy were achieved using a low-to-moderate daily maintenance dose of ICS, in keeping with current guidelines.[1,2] These findings are reassuring and suggest that this simplified treatment approach is unlikely to result in the overuse of medication in clinical practice. Further studies are required to determine how patient adherence is influenced by this novel strategy.

Since dose titration in this study was physician- and not protocol-driven, there is the risk of under-treatment – particularly in the salmeterol/fluticasone propionate group, where patients used only albuterol for rescue. However, asthma control in the salmeterol/fluticasone propionate group improved to a similar level reported in a recent study[7] involving patients receiving salmeterol/fluticasone 100/500 µg/day with upwards protocol-driven dose titration (without downward titration).

Further studies are required to determine how this single-inhaler therapy strategy influences asthma control among patients whose disease is of a more mild form. Given the moderate-to-severe nature of the patients studied in the COSMOS study, direct application to patients with less severe disease is not ideal. However, the report of Rabe et al.[27] suggests that budesonide/formoterol single-inhaler therapy is effective in patients with mild-to-moderate asthma. The findings of the COSMOS study[24] are consistent with the favorable efficacy and safety profiles of budesonide/formoterol maintenance and reliever therapy reported in several double-blind studies including more than 5000 patients,[22,23,26] and serve to validate the effectiveness of this new and simplified asthma treatment strategy.

4. Summary and Conclusions

The COSMOS study[24] clearly demonstrates that exacerbation burden is reduced more effectively when the budesonide/formoterol (single inhaler) combination is used for both maintenance and relief compared with FD therapy with salmeterol/fluticasone propionate and albuterol for rescue. The effectiveness of this strategy suggests that we will have to reconsider our definition of reliever therapy for patients who require long-term therapy with combination ICS and LABA medication. While the simplicity of this strategy appears almost too good to be true, its effectiveness and safety have been confirmed in several large studies involving thousands of patients.

To date the independent and/or complementary benefits of budesonide and formoterol with single-inhaler therapy have not been well described. Studies examining the short-term effects of ICS in asthma suggest that lung function may improve within 6 hours of administration of a single dose.[28,29] Gibson et al.[30] have shown that sputum eosinophil levels were significantly lower compared with placebo 6 hours after a single dose of budesonide, a finding that was also associated with a 2.2-fold improvement in airway responsiveness. Furthermore, the data from Spoelstra et al.[31] indicate that both budesonide and formoterol inhibit cytokine-induced adhesion molecule expression on human lung fibroblasts. Finally, Usmani et al.[32] have reported that combination therapy with fluticasone propionate and salmeterol augmented the action of fluticasone propionate on glucocorticoid receptor nuclear localization. Further studies are required to elucidate more precisely how the individual components of the single-inhaler strategy influence asthma control via independent and/or complementary pathways. The concept of single-inhaler maintenance and reliever therapy represents one of the most important advances in asthma management in many years, and one that appears particularly well suited for utilization in the primary care setting.

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